



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/852,958	05/10/2001	David A. Sirbasku	1944-00201	5333

7590

03/03/2005

David A. Sirbasku, ph.D.
Biopharma Global LLC
8714 West Royal Lane
Irving, TX 75063

EXAMINER

UNGAR, SUSAN NMN

ART UNIT

PAPER NUMBER

1642

DATE MAILED: 03/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/852,958	Applicant(s) SIRBASKU, DAVID A.	
	Examiner Susan Ungar	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 15 June 2004.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 4-10, 12-86, 95-101 and 109-122 is/are pending in the application.
- 4a) Of the above claim(s) 4-10, 12-33, 44-86, 96-101 and 115-122 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 34-43, 95 and 109-114 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>9/16/2002</u> . | 6) <input type="checkbox"/> Other: _____ |

2. The Election filed June 15, 2004 in response to the Office Action of October 3, 2003 is acknowledged and has been entered. Claims 1-108 were pending in the application, claims 1-3, 11, 87-94, 102-108 have been canceled, claims 34, 38, 44, 56, 63, 95, 99 have been amended and Claims 4-10, 12-33, 44-86, 96-101, 115-122 (all of whom are dependent upon claim 44 and are therefore joined to the group comprising claim 44) have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 34-43, 95, 109-114 are currently under prosecution.

3. Applicant's election with traverse of Group 10, claims 34-43 is acknowledged. The traversal is on the ground(s) that Groups 10, 11, 14, 15, 19, 20, 23 and 24 are all classified in Class 435, subclass 4 and therefore search of all of the claim together would not be unduly burdensome on the Examiner. The argument has been considered but has not been found persuasive because although the classification of the groups is the same, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive. Different searches and issues are involved in the examination of each group.

Applicant further argues that the methods of Groups 10, 13-15, 20 share steps, techniques and materials wherein the underlying assay methods and materials are similar and therefore the examination of all of the groups would not be an undue burden. The argument has been considered but has not been found persuasive because as previously set forth, the methods are distinct because they differ at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success and therefore examination of all of these group would be an undue burden.

Applicant further argues that the cell culture medium is useful in the methods of Groups 10, 11, 13, 14, 15, 19, 20, 23, 24 and is linked to the claims. The argument has been considered but has not been found persuasive, the cell culture medium is distinct and properly restricted from the claimed method for the reasons of record.

Applicant argues that the assay kits of claims 63-69 should be rejoined to Group 10 because claim 63 has been amended to require the culture medium of claim 45. The argument has been considered but has not been found persuasive because, for the reasons set forth above, the group comprising claim 45 has not been rejoined to Group 10.

Applicant reiterates argues drawn to Group 13, claim 56 and argues that claim 56 also provides for reversal of inhibition of thyroid hormone responsive cells by thyroid hormone. The arguments have been considered but have not been found persuasive for the reasons set forth above and further because the claim does not provide for reversal of inhibition by thyroid hormone but rather provides for optionally adding an inhibition reversing amount of thyroid hormone.

Applicant requests that the restriction requirement be redrawn in the light of the foregoing arguments and amendments. In light of the foregoing arguments and amendments, claim 95 has been rejoined with Group 10 and claims 109-114 as set forth above have been joined with Group 10. It is further noted that although claim 95 has been rejoined to Group 10, due to the amendment of the claim. However, claims 96-98 have not been rejoined because they are drawn to materially distinct methods which differ at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success from the method originally claimed and therefore are withdrawn from consideration and only the

invention constructively elected by original presentation for prosecution on the merits will be examined.

However, the remaining arguments have been considered but have not been found persuasive. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Applicant notes that in the Office Action of October 3, 2003 there is no Group 8 and claim 62 has not been assigned to a restriction group. Examiner apologizes for the inadvertent typographical error and hereby assigns claim 62 to Group 25.

Group 25 is drawn to a method of propagating a virus in the medium of claim 45 classified in Class 435, subclass 235.1. This Group is distinct from all of the other method groups because it is a materially distinct method which differs at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success.

The inventions of Groups 12 and 25 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (i) the process for using the product as claimed can be practiced with another materially different product or (ii) the product as claimed can be used in a materially different process of using that product [see *MPEP* § 806.05(h)]. In the instant case the cell culture medium as claimed can be used in a materially different process such as culturing hormone-responsive cell lines.

Given that Applicant has elected an invention for examination, given that Applicant has not traversed the lack of assignment of claim 62 to a restrictive group or requested the rejoined of claim 62 to the elected group, given that Examiner has assigned claim 62 to a specific Group and has explained the reasons

why the group is distinct, the omission of assignment of claim 62 has been remedied and Group 10 will be examined as set forth above.

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.8821 (a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reasons(s) set forth on the attached Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is given the period of reply for the instant paper within which to comply with the sequence rules, 37 CFR 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821 (g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for response beyond the SIX MONTH statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

In particular, figures 87 and 96 are drawn to unidentified sequences. Further, on page 15, para 0028 and page 150, para 0544, the specification discloses a special inhibitor motif of six amino acids which also does not comply with the sequence rules. Examiner has made an effort to identify these informalities but applicant must carefully review the specification to identify and indicate where other unidentified sequences may be found. Appropriate correction is required.

Specification

5. The specification on page 1 should be amended to reflect the status of the parent applications. Appropriate correction is required.

6. The specification is objected to because the Table of Contents recites paragraph numbers. These numbers must be deleted since they do not correspond to the paragraph numbers of the printed application and would not be expected to correspond to the paragraph numbers of an issued patent, if such patent were issued. Appropriate correction is required.

7. The specification is objected to because there are numerous instances of blank spaces wherein ATCC accession numbers and dates are missing from the disclosure, for example, see page 44, para 024. Further, there are numerous instances of blank spaces wherein US Application numbers and PCT numbers are missing from the disclosure, for example see p. 144, para 0528. Applicant is required to either amend the specification to include the information left out of the specification or to amend the specification to delete reference to the information. Appropriate correction is required.

8. The specification is replete with instances of grammatical and/or typographical errors, for example on page 73, para 0318 “culture medium acts is a weak estrogen”, page 129, para 0481 “an even more an important consequence”, page 129, para 0482). Examiner has made an effort to identify these informalities but Applicant must carefully review the specification to identify and indicate where these informalities can be found. Appropriate correction is required.

Trademarks

9. The use of the numerous trademarks has been noted in this application. Examples where trademarks are found are on p. 19, paragraph 0047, p. 55, paragraph 0275. However, the instances of trademarks are too numerous to detail here. Examiner has made an effort to identify these informalities but applicant must carefully review the specification to identify and indicate where recitations of

trademarks can be found. The trademarks be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 34-43, 95, 109-114 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 34-43, 95, 109-114 are indefinite because claim 34 is drawn to detecting steroid hormone-like cancer cell growth stimulation by a substance of interest. The claim is indefinite because the phrase “steroid hormone-like” is a relative phrase which renders the claim indefinite. The phrase “steroid hormone-like” is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In particular, as drawn to claim 95, since the specification, in paragraph 0052 of the published application, defines estrogenic as estrogen-like stimulation of cell proliferation, claim 95 is also

indefinite for the reasons set forth above drawn to “steroid hormone-like”. Further, it is noted that US Patent No. 5,135,849 specifically teaches that the term “androgenic” has no well defined meaning in the art and is conventionally used inconsistently and indiscriminately (col 7, lines 18-30) and that US Patent No. 4,859,585 specifically teaches that the term “estrogenic” has no well defined meaning in the art and is conventionally used inconsistently and indiscriminately (col 7, lines 35-45). Thus the art recognizes that phrases drawn to “estrogenic” androgenic” and by extension “steroid hormone-like” are indefinite.

Claims 34-43, 95, 109-114 are indefinite because claim 34 comprises the limitation “substantially devoid of unbound Fe(III). The claim is indefinite because the phrase “substantially devoid” is a relative phrase which renders the claim indefinite. The “substantially devoid” is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

12. If Applicant were able to overcome the rejection set forth above, Claims 34-39, 41-43, 95, 109-114 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting steroid hormone-like cancer growth stimulation by a subject of interest comprising maintaining a predetermined population of steroid hormone-responsive cells in a steroid hormone-free nutrient medium comprising a basal nutrient fluid substantially devoid of unbound Fe(III) and containing calcium ion and a quantity of immunoglobulin inhibitor sufficient to inhibit cell growth in the absence of an inhibition-reversing amount of steroid hormone wherein said immunoglobulin inhibitor is selected from the group consisting of dimeric/polymeric serum IgA,

polymeric IgM and IgG1 kappa or a combination thereof wherein a substance of interest is added and cell population is determined, does not does not reasonably provide enablement for a method of detecting steroid hormone-like cancer growth stimulation by a subject of interest comprising maintaining a predetermined population of steroid hormone-responsive cells in a steroid hormone-free nutrient medium comprising a basal nutrient fluid substantially devoid of unbound Fe(III) and containing calcium ion and a quantity of immunoglobulin inhibitor sufficient to inhibit cell growth in the absence of an inhibition-reversing amount of steroid hormone wherein a substance of interest is added and cell population is determined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is noted that in view of the indefinite nature of the claim language drawn to “steroid hormone-like cancer cell growth stimulation” in claim 34, it is assumed for examination purposes that steroid hormone-like cancer cell growth stimulation, claimed in claim 34 and the claims dependent thereon, is stimulation wherein the inhibitory action of immunological inhibitors of cell growth in steroid hormone-responsive cells is reversed.

The claims are drawn to a method of detecting steroid hormone-like cancer growth stimulation by a subject of interest comprising maintaining a predetermined population of steroid hormone-responsive cells in a steroid hormone-free nutrient medium comprising a basal nutrient fluid substantially devoid of unbound Fe(III) and containing calcium ion and comprising a quantity of immunoglobulin inhibitor sufficient to inhibit cell growth in the absence of an inhibition-reversing amount of

steroid hormone. This means any immunoglobulin inhibitor sufficient to inhibit cell growth in the absence of an inhibition-reversing amount of steroid hormone.

The specification teaches that the instant specification satisfies the long-felt needs for a sensitive way to screen substances for estrogenic and androgenic effects (page 15, para 0030). The specification teaches that since the early 1980's researchers have unsuccessfully tried to identify serum-borne inhibitors of steroid responsive cell growth and despite its first proposal more than fifteen years ago, the purified steroid reversible serum-borne inhibitor had not been previously described (pgs 2-4). Although patents have been issued drawn to a serum mediator that is a steroid reversible inhibitor of steroid responsive cell growth, the US Patents do not address the issues of whether there are one or more or disclose the exact chemical composition of the inhibitors (p. 6, para 0010).

The specification teaches that for the first time it is disclosed that, surprisingly, certain immunoglobulins exert a steroid hormone reversible negative regulatory effect on cancer cell growth (p. 16, para 0032). These immunoglobulin inhibitors have many immediate and potential applications as reagents for cell growth assays. For example, they are useful for *in vitro* testing of substances for estrogenic effects (or other steroid hormone-like effects) on steroid hormone responsive cell growth in a suitable assay system (p. 17, para 0039) and thus are useful for assaying agents of interest, such as drugs or environmental chemicals, for their steroid hormone-like effects on cell growth stimulation (p. 18, para 0042) as an aid to avoiding undesirable proliferative side effects of such drugs or substance *in vivo* (para bridging pages 19-20). The claimed method is useful for identifying substances that have unrecognized hormone-like properties that present health hazards (p. 36, para 0229).

As drawn to the broadly claimed immunoglobulin inhibitors, the specification teaches that IgA, IgM and certain IgGs provide negative regulation of steroid hormone responsive mucosal epithelial cancer cell growth (p. 15, para 0030) and for the first time it is disclosed, surprisingly, that certain immunoglobulins exert a steroid hormone reversible negative regulatory (inhibitory) effect on steroid responsive cancer growth. In the most preferred embodiments, the inhibitors is/are dimeric IgA (non-sIgA, polymeric IgM, IgG1 kappa and IgG2 (p. 16, para 0032). The specification exemplifies the chemical and immunological properties of the partially purified CA-PS-pool II of steroid hormone reversible inhibitors of cancer cell growth wherein the long sought after serum-borne cancer cell growth inhibitors were found to include at least IgA and IgM in Example 20, p. 124-129. The specification teaches that the series of investigations presented in the example demonstrate that a very longstanding problem has been solved (p. 129, para 0480), that is inhibitors have been identified. The specification teaches that dimeric/ polymeric plasma-derived IgA, but not serum monomeric IgA or sIgA, is a steroid hormone reversible inhibitor of steroid responsive cancer cell growth (p. 129, para 0481). The specification further teaches that plasma-derived multimeric IgM is a steroid hormone reversible inhibitor of steroid responsive cancer cell growth (p. 126, para 0472). The specification concludes the discussion of Example 20 and states that "This series of investigations demonstrate at least two immunoglobulin inhibitors in serum". There may still be other useful estrogen reversible inhibitors in serum that are yet to be identified from serum or tissue sources. The methods described in this Example have direct application to the search for new compounds that mimic the effect of the immunoglobulins as" steroid reversible inhibitors. (p. 130, para

0484). The specification teaches that a poly-Ig receptor or a poly-Ig like receptor mediates the inhibition of cell growth by IgA and IgM (p. 139, para 0514) but does not teach which poly-Ig receptor or poly-Ig like receptor could be used as target for development of compounds that mimic the immune system inhibition of cancer cell growth (pgs. 141-143).

The specification teaches that bulk purified mixtures of all subclasses of horse and rat IgG are not steroid hormone reversible inhibitors of steroid responsive cancer cell growth (p. 137, para 0510), but that additional studies demonstrated that IgG1 kappa alone was a significant steroid hormone reversible inhibitor of steroid responsive cancer cell growth. Although experiments with prostate cancer cells lines showed some steroid hormone reversible inhibition of steroid responsive cancer cell with IgG2 kappa the data was not shown (p. 138, para 0511) and it does not appear that this effect was significant as the discussion of Example 23 did not even mention IgG2 kappa. This discussion however, clearly discloses that the preference for the kappa light chain implies that a different receptor mediates the effects of this immunoglobulin as compared to IgA and IgM (p. 138 para 0512) and concludes that once it is identified, the receptor that mediates the IgG1 growth inhibition effect will provide another target for development of compounds that mimic the immune system inhibition of cancer cell growth (p. 138, para 0512).

One cannot extrapolate the teaching of the specification to the enablement of the claims because the specification clearly and repeatedly teaches that the identification of the immunoglobulin inhibitors was a "surprising" that is, an unexpected event and that fifteen years of combined research by those skilled in the art had failed to identify serum-borne inhibitors of steroid responsive cell

growth and despite its first proposal more than fifteen years ago, the purified steroid reversible serum-borne inhibitors had not been previously described. Further, although patents have been issued drawn to a serum mediator that is a steroid reversible inhibitor of steroid responsive cell growth, the US Patents do not address the issues of whether there are one or more or disclose the exact chemical composition of the inhibitors. However, the instant specification only sets forth three immunoglobulin inhibitors that in fact are effective as the steroid reversible immunoglobulin inhibitors of steroid-responsive cell growth. The identification of these three factors does not predictably enable the claimed invention because the specification does not teach how to make the claimed invention. Although it appears that the binding of the inhibitory immunoglobulins is through the Fc portion of the immunoglobulins, there is no teaching of which structures of the Fc portions are required for the invention to function as claimed. The specification clearly teaches that the preference for the kappa light chain of IgG implies that a different receptor mediates the effects of this immunoglobulin as compared to IgA and IgM. The specification further teaches that a (emphasis added) pIgR is the target for IgA and IgM but does not identify which pIgR is the target for steroid hormone reversible inhibition. However, the specification provides no information as to structures that are common to the exemplified inhibitors that would allow one of skill to predictably make the claimed inhibitors based on a structure/function correlation. Although the specification clearly teaches that once the receptors are identified, the receptors will provide another target for the development of compounds that mimic the immune system inhibition of cancer cell growth, there is no guidance as to the receptors to which the inhibitory immunoglobulins bind so that one could make inhibitors that would predictably mimic the immune system

inhibition of cancer cell growth. Finally, although the specification teaches that there may still be other useful steroid reversible inhibitors in serum that are yet to be identified from serum or tissue sources, the specification provides no guidance as to how one would predictably identify these other useful steroid reversible inhibitors.

The specification does not teach how to extrapolate the teaching of the three identified inhibitors to the broadly claimed invention because the specification does not provide information that could be used to predictably distinguish tissue inhibitory immunoglobulins from those that are not inhibitory and the screening assays exemplified in the specification for identification and testing of inhibitory immunoglobulins do not meet the standard of 35 USC 112, first paragraph because they do not teach how to make the claimed invention.

Applicant is reminded that 35 USC 112, first paragraph does not require that the specification teach how to screen for inhibitors, but rather requires that the specification teach how to make and use the claimed invention. In particular, screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention. It is clear that in the absence of an effective steroid reversible inhibitor, one would not be able to successfully use the claimed broadly claimed invention.

Given that the specification specifically teaches that the combined research of those of skill was not successful in identifying the claimed immunological inhibitors despite 15 years of research, given that the specification teaches the surprising nature of the claimed inhibitors, given that the specification teaches that

the receptors to which the immunological inhibitors bind are unknown, given that the specification does not teach, other than through screening assays how to identify the claimed invention, since the structures involved with the binding of the inhibitors to their cognate receptors are unknown, it is clear that the specification does provide the necessary guidance to one of skill to enable the making of the claimed invention and if the making of the broadly claimed invention is not enabled, one would not know how to use the broadly claimed invention.

The specification provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predictably make the claimed invention so that it would function as claimed with a reasonable expectation of success. In the absence of guidance or exemplification so that the broadly claimed immunological inhibitors could be predictably made, the screening assays taught are drawn only to a wish or a plan for making the claimed invention. For the above reasons, it appears that undue experimentation would be required to enable one to practice the claimed invention.

13. Claims 34-39, 41-43, 95, 109-114 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 34- 39, 41-43, 95, 109-114 are drawn to steroid reversible inhibitors of steroid hormone-responsive cell growth. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

The court stated that “[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials. *Id.* At 1567, 43 USPQ2d at 1405.

The court also stated that

a generic statement such as “vertebrate insulin cDNA” or “mammalian insulin cDNA without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that “naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. *Id.*

Finally, the court addressed the manner by which a genus of cDNAs might be described. “A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Id.*

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that “the written description

requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristicsi.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of steroid reversible inhibitors of steroid hormone-responsive cell growth, per Lilly by structurally describing a representative number of steroid reversible inhibitors of steroid hormone-responsive cell growth or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus. Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

In this case, the specification does not describe the steroid reversible inhibitors of steroid hormone-responsive cell growth required to practice the claimed method in a manner that satisfies either the Lilly or Enzo standards. The IgG1 kappa inhibitor disclosed does not appear to share a relevant structure with polymeric/multimeric IgA or multimeric IgM. In addition, given the surprising

nature of the discovery, the combination of the polymeric/multimeric IgA and the multimeric IgM do not provide a representative number of immunological inhibitors that would meet the requirements of Lilly. Further, the specification does not provide any functional characteristics coupled with a known or disclosed correlation between structure and function as drawn to the inhibitory activity. Although the specification discloses three effective immunological inhibitors, this does not provide a description of the steroid reversible inhibitors of steroid hormone-responsive cell growth that would satisfy the standard set out in Enzo, or describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus which would satisfy the standard set out in Lilly."

Since the specification fails to adequately describe the broadly claimed steroid reversible inhibitors of steroid hormone responsive cell growth, it also fails to adequately describe the assay method of using the claiming invention.

14. In the interests of compact prosecution, if Applicant were to amend the claims to recite further clarify the claimed inhibitors, for example to recite the limitation "comprising a steroid hormone reversible inhibitor, wherein said inhibitor consists of an immunoglobulin or a combination of immunoglobulins", and if Applicant were able to overcome the rejections under 35 USC 112, first and second paragraph above, Claims 34-43, 95, 109-113 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed method of detecting steroid hormone-like cancer growth stimulation by a subject of interest comprising maintaining a predetermined population of steroid hormone-responsive cells in a defined steroid free nutrient medium comprising 1.0 ng/mL to 10 ng/mL insulin, 0.3 - 10 nM triiodothyronine, 2 - 50

ug/mL- diferric transferrin, 5 - 100 gM elhanolamine, 0.2 - 5.0 mg/mL- bovine serum albumin (BSA), 5 - 20 ng/mL - selenium, 2 - 10 MM deferoxamine, and depending upon the requirements of the selected cells to be cultured, at least one compound chosen from the group consisting of 1 - 50 ng/mL EGF, 0.2 - 20 ng/mL - aFGF, 5 - 50 MM phosphoethanolamine, 50 - 500 ug/mL linoleic acid-BSA, 1 - 50 ug/mL reduced glutathione, 0.5 - 2.0 mM glutamine, 1 - 10 ug/mL heparin, and 20 - 50 ug human fibronectin (per 35-mm diameter culture dish) wherein the nutrient medium further comprises no more than about 1 uM unbound Fe(III) and contains about 1-50 mM calcium ion does not reasonably provide enablement for the claimed method of detecting steroid hormone-like cancer growth stimulation by a subject of interest comprising maintaining a predetermined population of steroid hormone-responsive cells in a steroid free nutrient medium wherein said medium comprises a basal nutrient fluid substantially devoid of unbound Fe(III) and containing calcium ion. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is noted that in view of the indefinite nature of the claim language drawn to "steroid hormone-like cancer cell growth stimulation" in claim 34, it is assumed for examination purposes that steroid hormone-like cancer cell growth stimulation, claimed in claim 34 and the claims dependent thereon as well as the estrogen-like cancer growth stimulation claimed in claim 95, is stimulation wherein the inhibitory action of immunological inhibitors of cell growth in steroid hormone-responsive cells is reversed.

The claims are drawn to a method of detecting steroid hormone-like cancer growth stimulation by a subject of interest comprising maintaining a predetermined

population of steroid hormone-responsive cells in a steroid free nutrient medium wherein said medium comprises a basal nutrient fluid substantially devoid of unbound Fe(III) and containing calcium ion. This means any medium as long as it is a basal nutrient fluid substantially devoid of unbound Fe(III) and it contains calcium ion.

The specification teaches that in order to grow the cells used in the presently described studies, the formulations of serum-free defined medium employed are specific optimizations, modifications, or necessary changes of earlier media that have been described (p. 89, para 0355). The formulations presented permit dissection of growth into its individual parts caused by different stimulators. Said serum-free medium provides a tool for the assessment of growth inhibitors isolated from horse serum whose actions are reversed by sex-steroid hormones. Thus the serum-free media raises the hope for the provision of a new insight that could help to clarify the mechanisms involved in the control of breast, prostatic and other mucosal cancers under conditions not previously available (p. 95, para 0374).

The specification teaches that it is widely believed that the phenol red indicator in tissue culture medium acts as a weak estrogen and at the concentration in standard culture media, it was believed to stimulate ER+ cell growth nearly as well a natural estrogens (para 0318). However, using the defined steroid free nutrient medium taught in the specification it was possible to determine that the concentration of phenol red contaminants in a standard culture medium today is not sufficient to cause estrogenic effects. Demonstration of sex hormone mitogenic effects in culture depends upon conditions that maximize the effects of a serum-borne inhibitor as described in the Examples. When the effects of the inhibitor are optimized, the presence or absence of phenol red makes no everyday

difference to the demonstration of estrogen mitogenic effects with several target cell types from diverse species (p. 74, para 0319). The specification specifically teaches the composition of serum free defined media and serum-free media variations in TABLE 7 and on pages 93-94. Further the specification teaches that the media described in TABLE 7 were optimized for the specific cell types designated. Additionally, they were optimized to permit direct comparison of the growth properties of ER+ and AR+ steroid hormone sensitive tumor cell lines to their ER- and AR- steroid hormone insensitive counterparts. This careful optimization was done originally to study rat mammary tumor cells. The specification discloses that previously, there was a defined medium for the prostate cancer cell line PC3, but that this medium was evaluated and did not support LNCaP prostate cancer cell line growth. Although other have reported “serum-free’ media that was stated to be effective with the LNCaP cell lines, the problem was that this medium was not serum-free nor was it defined. Under those conditions, an accurate analysis of hormonal and growth factor effects cannot be done satisfactorily (p. 98). The new serum-free defined medium serves as part of a model system for identifying physiologically relevant new molecules. When completely serum-free defined conditions were employed in the past, the effects of estrogens were either marginal or insignificant (p. 104, para 0399).

One cannot extrapolate the teaching of the specification to the scope of the claims because the specification clearly teaches that the “new” serum-free defined medium is a critical element of the claimed invention. The specification clearly teaches that in order to grow the cells used in the presently described studies, the formulations of serum-free defined medium employed are specific optimizations, modifications, or necessary changes of earlier media that have been described and

that the formulations presented permit dissection of growth into its individual parts caused by different stimulators and exemplifies the inability of standard culture media to permit dissection of growth into its individual parts caused by different stimulators. In particular, the specification teaches that when completely serum-free defined conditions were employed in the past, the effects of estrogens were either marginal or insignificant. Specifically, the new media were carefully optimized to permit direct comparison of growth properties of ER+ and AR+ steroid hormone sensitive tumor cell lines and their ER- and AR- steroid hormone insensitive counterparts. Further, the specification teaches that although others have reported “serum-free” media that was stated to be effective, for example, for growing the LNCaP prostate cancer cell line, the problem with this medium was that it was not in fact serum-free, nor was it defined. Under those conditions, an accurate analysis of hormonal and growth factor effects **cannot** (emphasis added) be done satisfactorily. The new serum-free defined medium serves as part of a model system for identifying physiologically relevant new molecules. Although the specification specifically states that the formulations of serum-free defined medium employed are specific optimizations, modifications, or necessary changes of earlier media that have been described and that the formulations presented permit dissection (for the first time) of growth into its individual parts caused by different stimulators, the specification provides only a single example of a medium that will function as claimed with defined variations depending upon the requirements of the selected cells to be cultured but does not teach how to successfully use the claimed invention with any other medium. This is critical because the specification specifically teaches that when completely serum-free defined conditions were employed in the past, the effects of estrogens were either

marginal or insignificant and that in the absence of the defined medium, an accurate analysis of hormonal and growth factor effects **cannot** (emphasis added) be done satisfactorily. It is clear that in years of research, no other media/defined media has been found to be effective to function as claimed. The single example of a steroid hormone-free nutrient medium, modifiable for specific cell lines, does not provide guidance for how one would make any other medium that produces conditions that maximize the effects of a serum-borne inhibitor as described in the Examples. Although experimentation to provide optimization is not considered undue, the specification does not teach the “necessary” changes of earlier media that are required so that one could make a medium that would function as claimed. Thus, the specification does not provide guidance on how one would make the claimed invention. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention in the absence of the defined medium taught in the specification.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 34-42, 95, 109-112 are rejected under 35 U.S.C. § 102(b) as being anticipated by US Patent No. 5,135,849.

The claims are drawn to an *in vitro* method for detecting steroid hormone-like cancer cell growth stimulation by a substance of interest comprising

maintaining a predetermined population of steroid hormone-responsive cells in a steroid hormone-free basal nutrient medium substantially devoid of unbound Fe(III) and containing calcium ion comprising a quantity of immunoglobulin inhibitor sufficient to inhibit cell growth in the absence of an inhibition-reversing amount of said steroid hormone, said cells being steroid hormone dependent for proliferation in vivo, adding said substance of interest to said cells, incubating and determining the cell population wherein a measurable increase in said cell population indicates a steroid hormone-like cell growth stimulating effect by said substance of interest (claim 34), comprising maintaining serum-free assay conditions (claim 35), comprising adding steroid-hormone depleted serum to said nutrient medium (claim 36), further comprising obtaining non-heat inactivated serum containing said immunoglobulin inhibitors (claim 37), wherein said immunoglobulin inhibitor comprises at least one secretory immunoglobulin chosen from the group consisting of dimeric/polymeric IgA, polymeric IgM and IgG (claim 38), wherein at least one secretory immunoglobulin is chosen from the group consisting of IgG1 and IgG2 (claim 39), wherein at least one secretory immunoglobulin is IgG1kappa (claim 40), wherein said substance contains or is suspected of containing proteolytic activity, the method comprising selecting an immunoglobulin inhibitor that resists protease degradation (claim 41), wherein said selected immunoglobulin inhibitor comprises IgA2 (claim 42), said method using a population of estrogen-responsive cells, whereby an estrogen-like cell growth stimulating effect by said substance is detected and whereby an estrogenic substance is detected (claim 95), whereby said steroid hormone free nutrient medium comprises no more than about 1 micromolar unbound Fe(III) (claim 109), wherein the medium comprises a Fe(III) chelating agent (claim 110), wherein the

medium comprises a cell attachment promoting protein (claim 111), whereby said medium contains about 1-50 mM calcium ion (claim 112).

It is noted that in the absence of a definition for inactivated serum, it is assumed for examination purposes that inactivated serum means serum that has had active ingredients, such coagulation factors, removed.

US Patent No 5,135,849 specifically teaches an *in vitro* method for detecting steroid hormone-like cancer cell growth stimulation by a substance of interest (wherein said substances produces, emulates or mimics the effect of naturally occurring endogenous steroid hormone [col 8, lines 12-15]) comprising maintaining a predetermined population of steroid hormone-responsive LNCaP cells in a steroid hormone-free basal nutrient medium substantially devoid of unbound Fe(III) and containing calcium ion (Dulbecco's Eagle's Minimal Essential Medium, claim 6 wherein said medium is substantially devoid of Fe(III), that is approximately .25 micromolar, and comprises approximately 1.25 mM calcium as per Invitrogen catalogue) wherein the medium comprises a quantity of inhibitor of androgen dependent cell proliferation which is endogenous to the serum of humans or animals sufficient to inhibit cell growth in the absence of an inhibition-reversing amount of said steroid hormone, said cells being steroid hormone dependent for proliferation *in vivo*, adding said substance of interest to said cells, incubating and determining the cell population wherein a measurable increase in said cell population indicates a steroid hormone-like cell growth stimulating effect by said substance of interest, (claim 1) that is the overcoming of the inhibition of androgen stimulated cell proliferation, wherein functional equivalents of charcoal dextran stripped human serum are used in the assay, that is the inhibitor is semi-purified (cols 19-20) and thus the maintaining medium is in

fact serum free, comprising adding steroid-hormone depleted serum to said nutrient medium (claim 7), further comprising obtaining non-heat inactivated serum containing said immunoglobulin inhibitors (see column 20 wherein heat inactivated serum, that is serum which has had the coagulation factors removed, is obtained). The specification further teaches that the serum born inhibitor is found in the sera of male and female humans, bovines, horses, pigs, dogs, rats and mice and that it is heat stable (col 10, lines 61-70). Although the prior art specification does not specifically teach that the inhibitor comprises immunoglobulins, secretory immunoglobulin chosen from the group consisting of dimeric/polymeric IgA, polymeric IgM and IgG, IgG1 and IgG2, IgG1 kappa, IgA2, given that the instantly claimed immunoglobulin inhibitors are isolated from serum wherein the prior art reference specifically teaches that the serum borne inhibitor is found in male and female humans, bovines, horses, pigs, dogs, rats and mice, it is clear that at least a subset of the inhibitor components include all of the claimed immunoglobulin inhibitors since these are ubiquitously found in serum and thus at least a subset of the inhibitor components of the prior art reference appears to be the same as the instantly claimed immunoglobulin inhibitors. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from that taught by the prior art and to establish patentable differences. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Further, the method of the prior art comprises the same method steps as claimed in the instant

invention, that is, assaying for steroid-hormone like effects of substances of interest comprising assaying the same population of cells with a medium comprising a serum borne inhibitor found in male and female humans, bovines, pigs, dogs, rats, mice and horses from which the instantly claimed immunoglobulins were isolated, thus the claimed method is anticipated because the serum borne inhibitor inherently comprises the claimed immunoglobulin inhibitors. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). It is noted that, because of structural differences, IgA2 lacks sites required for proteolysis (see (Chintalacharuvu K R and Morrison S L (1996) J Immunol 157, 3443-3449 cited in the specification) thus would clearly resist protease degradation.

In addition, the specification teaches that the LNCaP cells are estrogen-responsive, see Figure 2 and demonstrates the growth stimulating effect of an estrogenic substance wherein the estrogenic substance is detected (see Table 1). Finally, upon addition of the charcoal dextran stripped serum, the assay medium comprises the proteins of the serum wherein serum is well known to contain both apotransferrin, an effective Fe (111) chelator (see Eby et al (1992, Anal Biochem, 203,317-325 cited in the specification) and fibronectin, a cell attachment promoting protein (see Tr. J of Medical Sciences, 1998, 28:383-387, see in particular the abstract and page 383, col 1, page 386, para bridging cols 1 and 2). All the limitations of the claims are met.

It is noted that the specification admits on the record that patents have been issued drawn to an uncharacterized serum mediator that is steroid hormone reversible in steroid responsive cells and points specifically to US Patent No. 5,135,849. Given the broadly written claims, the US Patent reads on the claimed invention for the reasons set forth above. The rejection can be obviated by

amending the claims to recite, for example, “comprising a steroid hormone reversible inhibitor, wherein said inhibitor consists of an immunoglobulin or a combination of immunoglobulins”.

Claim Objections

17. Claim 37 is objected to because although the claim is drawn to the method of claim 34 further comprising obtaining non-heat inactivated serum containing said immunoglobulin inhibitors. However, there are no method steps recited for the obtaining non-heat inactivated serum. There appears to be a typographical error, does Applicant intend to claim the method of claim 34 further comprising adding non-heat inactivated serum containing said immunoglobulin inhibitors?

Appropriate correction is required.

18. Claims 41 is objected to because there is no antecedent basis for the recitation of “the method comprising selecting an immunoglobulin” in claim 34 from which it depends. The objection could be obviated by amending the claim, for example to recite “the method further comprising selecting an immunoglobulin.”

19. Claims 34-43, 109-113 and 114 are objected to as being dependent upon non-elected claim 45. The rejection can be obviated by amending claim 34 to recite all of the limitations of claim 45 and deleting reference to claim 45.

20. Please note that the none of the references disclosed on the IDS forms submitted 6/7/04 or 4/4/03 have been considered because the references were not found in the file. If the references were indeed submitted, Examiner would appreciate the resubmission of these references so that they can be considered.

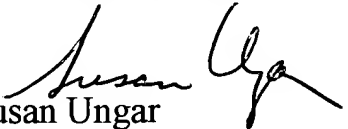
21. No claims allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is

Art Unit: 1642

(571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The fax phone number for this Art Unit is (571) 273-8300.



Susan Ungar

Primary Patent Examiner

February 9, 2005